REMARKS

Status of the claims

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-63 are pending in the application. Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-63 stand rejected.

Claim 1 is amended. Claims 62 and 63 are canceled. No new matter has been added.

Amendments to the claim

Claim 1 has been amended to state "...wherein said diuretic(s) inhibits reabsorption of Actinium-225 daughters and preventing accumulation of francium-221 and bismuth-213 daughters within the kidneys thereby reducing nephrotoxicity during the radioimmunotherapeutic treatment." This is intended to over the 35 U.S.C. §112 rejection.

The 35 U.S.C. §112 rejection

Claims 1-2, 4-5, 8-12 and 62 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicants respectfully traverse this rejection.

The Examiner states that claim 1 recites a method of reducing the nephrotoxicity in an individual during radioimmunotherapeutic treatment of a pathological condition comprising: administering a pharmacologically effective dose of one or more diuretics and chelated actinium-225 radioimmunoconjugate, wherein interaction between said diuretics prevents accumulation of francium-221 and bismuth-213 daughters in the kidney. The Examiner asserts that it is unclear whether the diuretics interact with themselves or with the francium-221 and bismuth-213.

The Applicants have currently amended independent claim 1 to state "...wherein said diuretic(s) inhibits reabsorption of Actinium-225 daughters and

preventing accumulation of francium-221 and bismuth-213 daughters within the kidneys thereby reducing nephrotoxicity during the radioimmunotherapeutic treatment" thus, removing any ambiguity regarding the action of the diuretics. In view of the amendment, the Applicants respectfully request that the rejection of claims 1-2, 4-5, 8-12 and 62 under 35 U.S.C. §112 be removed.

The 35 U.S.C. §103 rejection

Claims 1-2, 4-5, 8, 10-11, 49, 51-53, 59-60 and 62-63 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al.* (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244) in view of **Satoh** *et al.* (Eur. J. Cancer Clin. Oncol. 1989; 25: 1727-1731), **Jones** *et al.* (Nuclear Medicine & Biology 1996; 23: 105-113), and **Schilcher** *et al.* (J. Can. Res. Clin. Oncol. 1984; 107: 57-60) in further view of **Nair** *et al.* (J. Radiat. Res. 2001; 42: 21-37).

The Examiner states in the Office Action that **Kennel** *et al.* teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate. The Examiner also states that while **Kennel** *et al.* teach isotope coupled to the targeting monoclonal antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy. As an example, the Examiner points out that **Kennel** *et al.* teach at necropsy, animals had total ablation of bone marrow cells, splenic atrophy, some damage to the lining of their stomachs and intestine and excess accumulation of undigested food in their stomachs. The Examiner does state that **Kennel** *et al.* do not explicitly teach administering a competitive metal blocker such as bismuth subnitrate, a chelator such as DMPS or a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

The Examiner states that **Satoh** *et al.* teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ-ray irradiation in mice. The Examiner also states that **Satoh** *et al.* teach that oral administration of BSN reduced the lethal effects

and bone marrow damage by γ-ray irradiation without compromising the tumor-reducing effect. The Examiner concludes that **Satoh** *et al.* teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy.

The Examiner states in the Office Action that **Jones** *et al.* teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal. The Examiner also states that **Jones** *et al.* teach that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal folding proteins. The Examiner further states that **Jones** *et al.* disclose the evaluation of dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA) for their use as adjuvants to reduce or prevent radiotoxicity of Lead-212 or Bismuth-212 alpha-radioimmunotherapy.

The Examiner states in the Office Action that **Schilcher** *et al.* teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors. The Examiner states in the Office Action that **Nair** *et al.* teach radioprotector in radiotherapy and that the use of nontoxic amounts of radioprotectors having a different mechanism of action can overcome the problems with their toxicity.

The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the references so as to modify the methods taught by **Kennel** *et al.* to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** *et al.*, **Schilcher** *et al.* The Examiner asserts that one would have been motivated to do so because each of

the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Furthermore, the Examiner states that as taught by **Nair** *et al.*, combining several radioprotectors having a different mechanism of action can overcome the problems associated with radioprotector toxicity. Thus, the Examiner concludes that one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by **Kennel** *et al.* to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** *et al.* and **Shilcher** *et al.*, one would achieve a method for reducing the accumulation of 213Bi in the kidney, as well as bone marrow damage. The Applicants respectfully disagree.

The Applicants submit that **Kennel** *et al.* disclose evaluation of Ac-225 for vascular targeted radioimmunotherapy of lung tumors and conclude that the potential for Ac-225 as radioimmunotherapeutic agent is compromised most prominently by the radiotoxicity associated with the decay daughter radioisotopes released from the target organ (Abstract). **Kennel** *et al.* further disclose that they know of no conventional chelate that could withstand the energy released by radioactive decay of Ac-225 (pg 243, col. 1, lines 2-4).

Satoh *et al.* disclose that the preinduction of metallothionein by oral administration of bismuth subnitrate may reduce the adverse effects of gamma ray irradiation in mice (Abstract). A dose of 200 mg/kg prior to irradiation with a lethal dose of 6 Hy/leg of cobalt-60 suppressed leukocyte reduction and lipid peroxidation in bone marrow cells and increased metallothionein 2-fold therein (pg 1728, col. 2). It is assumed that bismuth subnitrate induces an increased level of metallothionein which scavenges the free radicals induced by the gamma irradiation and thereby protects the bone marrow from gamma radiation injury (pg 1729, col. 2 to pg 1730 col. 1, II. 2).

Jones *et al.* disclose that DMPS, which is more effective than DMSA, can be used as a potential adjuvant chelation therapy in lead-212 or bismuth-212 radioimmunotherapy protocols (Abstract). **Schilcher** *et al.* examines the effect of

fractionated low and single high dose cisplatin in various tumors. **Schilcher** *et al.* state that cisplatin therapy was associated with nephrotoxicity (pg 59, col 2) and that cumulative nephrotoxicity was prevented by prehydration and/or treatment with furosemide or mannitol (Summary) although **Schilcher** *et al.* do not support this assertion with any actual data. In fact, nephrotoxicity associated with the cisplatin therapy was observed in only three patients (pg 59, col 1, 2).

Nair *et al.* review radioprotecting agents categorized as radioprotectors, adaptogens and adsorbents (pg 22) and hypothesize that using non-toxic amounts of several agents might overcome the toxicities associated with larger doses required when used individually (pg 31).

In order for an obviousness rejection to be valid, the combined references must reasonably teach each and every element of the pending claim. Furthermore, the references must also provide motivation for one of ordinary skill to make the combination with a reasonable expectation of success. The Applicants respectfully submit that **Kennel** *et al.* specifically state that although HEHA-chelated actinium-225 coupled to a targeting antibody may deliver a tumoricidal dose to the lung, the radiologic side effects due to release of daughter alphas limits the effectiveness of the therapy. **Kennel** *et al.* also state that they know of no conventional chelant that would withstand the energy release (pg 242, col. 2). Secondly, **Kennel** *et al.* is deficient in that it is silent with respect to ways of reducing the radiologic side effects attributable to the release of alpha particles from the Ac-225 and the daughters. Specifically, the reference neither teaches nor suggests using a diuretic concomitantly with the Ac-225 antibody construct to reduce nephrotoxicity caused by Fr-221 and Bi-213 release of alpha particles.

The deficiency of **Kennel** *et al.* is not remedied by any of the supplementary references, alone or in combination, provided for by the Examiner. In particular, none of the references teach an Ac-225-MAb conjugate or administering the same as a randiommunotherapeutic against a pathophysiological condition.

The Applicants respectfully submit that **Satoh** *et al.* primarily disclose prevention of adverse effects of gamma ray irradiation while the present invention is

directed primarily to prevention of adverse effects of alpha particle-emitting elements during radioimmunotherapy. Furthermore, **Kennel** *et al.* is primarily related to treating lung cancer with alpha particles. Thus, it is unlikely that a person of ordinary skill would be inclined to combine the teachings of **Satoh** *et al.* and **Kennel** *et al.* since they pertain to different subject matter altogether and additional experimentation would be needed before any conclusions about alpha particles can be made.

The Applicants also submit that **Jones** *et al.* only disclose Bismuth-212 as a potential target of DMPS/MSA adjuvant chelation therapy. By contrast, the claimed invention is directed to targeting both Bismuth-212 and Francium-221. When evaluating obviousness, each and every word of a claim must be considered. In this case, since the claim is directed to a method of reducing nephrotoxicty resulting from Ac-225 daughters, Fr-221 and Bi-212, the combination of **Kennel** *et al.* and **Jones** *et al.* would clearly not produce the claimed invention.

The Applicants respectfully submit that **Schilcher** *et al.* do not teach or suggest using a diuretic to prevent nephrotoxicity from a radiometal. **Schilcher** *et al.* only state that cumulative nephrotoxicity from cisplatin chemotherapy was prevented by treatment of the diuretic furosemide, but do not provide any guidance for its use. Furthermore, the platinum in cisplatin is not a radiometal and the nephrotoxicity from cisplatin is due to the platinum whereas the nephrotoxicity of Ac-225 administration is due to the alpha particle emissions from Fr-221 and its daughter Bi-213 in the kidneys. In fact, the toxicity from platinum is from the heavy metal poisoning of the kidney cells whereas the toxicity in the present application is from alpha particles which is neither a metal nor even an atom. The subject matters are entirely different altogether. Thus, there would be no motivation for a person of ordinary skill in the art to combine the teachings of **Kennel** *et al.* and **Schilcher** *et al.*

In addition, the Applicants submit that **Nair** *et al.* neither teach nor suggest that diuretics are radioprotector compounds. Furthermore, nothing in the references presented suggests that diurectics are radioprotector compounds nor is it common knowledge. Thus, the combination of **Nair** *et al.* with the references

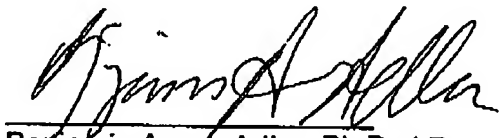
presented by the Examiner would not render the claimed invention obvious since Nair et al. specifically do not teach the use of diuretics to lower nephrotoxicity.

In view of the arguments presented herein, the Applicants respectfully request that the rejection of claims 1-2, 4-5, 8, 10-11, 49, 51-53, 59-60 and 62-63 under 35 U.S.C. §103 be removed. The Applicants believe that the claims are now in condition for allowance.

This is intended to be a complete response to the Office Action mailed January 7, 2009. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: May 20, 2009



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